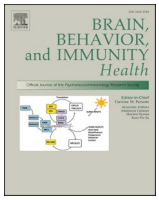
Brain, Behavior, & Immunity - Health 40 (2024) 100830

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Considering the role of estradiol in the psychoneuroimmunology of perimenopausal depression

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A B S T R A C T

In recent years, a burgeoning field of research has focused on women's mental health and psychiatric conditions associated with perinatal and postpartum periods. An emerging trend points to the link between hormone fluctuations during pregnancy and postpartum that have immunologic consequences in cases of perinatal depression and postpartum psychosis. The transition to menopause (or "perimenopause") has garnered comparatively less attention, but existing studies point to the influential interaction of hormonal and immune pathways. Moreover, the role of this cross talk in perturbing neural networks has been implicated in risk for cognitive decline, but relatively less work has focused on the depressed brain during perimenopause. This brief review brings a psychoneuroimmunology lens to depression during the perimenopausal period by providing an overview of existing knowledge and suggestions for future research to intertwine these bodies of work.

1. Introduction

In recent years, researchers have sought to better understand the biological underpinnings of reproductive-related mental health concerns. For example, the role of psychoneuroimmunology has been increasingly implicated in perinatal and postpartum psychiatric conditions (Anderson and Maes, 2013; Fransson, 2021; Hazelgrove, 2021). Observational and experimental studies point to the interaction of reproductive hormones and inflammatory changes as potential contributors to perinatal depression (Balan et al., 2023; Szpunar et al., 2021), and novel treatments act on immune-related pathways (Balan et al., 2023; Patterson et al., 2023). Despite this burgeoning line of research focused on maternal mental health, less light has been shed upon other reproductive transitions characterized by hormonal fluctuations. In particular, depression that emerges during the menopause transition, or "perimenopause," negatively impacts quality of life (Whiteley et al., 2013). Similar to pregnancy, perimenopause is a period of marked fluctuations in hormones, as well as immunologic changes that act upon the brain and other biological systems (Barth and de Lange, 2020). However, compared to perinatal depression, less is known about psychological and biological factors that influence perimenopausal-onset depression. In this brief review, the case is made for similarly investigating the psychoneuroimmunology of depression during perimenopause, which may uncover avenues for diagnosis and treatment.

2. What is perimenopause?

Perimenopause is an umbrella term to describe the transition to reproductive senescence, or menopause (Harlow et al., 2012; Santoro, 2016). Typically lasting 5–6 years, perimenopause is characterized by changes to menstrual cycle length and fluctuations in female sex hormones like estradiol (E2), a primary form of estrogen, (Gordon and Sander, 2021). Menopause is reached one year following the final menstrual period and is marked by largely depleted E2 levels. Individuals in perimenopause may experience hot flashes, sleep difficulty, cognitive impairment, and sexual concerns (Monteleone et al., 2018; Woods and Mitchell, 2005), and studies suggest depression risk increases during this time compared to pre-menopause (Bromberger et al., 2011; Bromberger and Epperson, 2018; de Kruif et al., 2016; Freeman et al., 2006). Risk for depression onset during perimenopause has been linked to several factors, including sensitivity to the volatile fluctuations of E2 (Gordon et al., 2019; Gordon and Sander, 2021; Maki et al., 2018). However, few studies have further investigated this purported link and the potential interplay with psychoneuroimmunology, and more research is needed to better understand the dynamics underlying depression onset during perimenopause.

3. Perimenopause as time of increased immune activity

Natural aging has been linked to systemic elevations in inflammation as the immune system functioning declines (Goetzl et al., 2010). Coinciding with this phenomenon in women is the decline in reproductive

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https://doi.org/10.1016/j.bbih.2024.100830
Received 30 November 2023; Received in revised form 24 June 2024; Accepted 20 July 2024
Available online 21 July 2024

function and transition to menopause (Barth and de Lange, 2020). Indeed, previous studies have identified increased circulating levels of pro-inflammatory cytokines in postmenopausal women compared to premenopausal women (Figueroa-Vega et al., 2015; A. Han et al., 2021; Malutan et al., 2014; Pfeilschifter et al., 2002; Vural et al., 2006). Table 1 summarizes the main studies discussed in this section and highlights inconsistencies in the associations between specific symptoms in perimenopause and menopause with inflammatory and metabolic markers. Studies often assess a host of various pro- and anti-inflammatory cytokines, proteins, and genes implicated in inflammatory and immune processes. This inconsistency in markers selected may contribute to lack of replicated findings. However, several studies include a common probe of inflammatory responses, the acute phase reactant C-reactive protein (CRP). Serum levels of CRP show conflicting associations with depressive symptoms over peri- and post-menopause. Some studies have found elevated CRP in those with greater depression, while others have failed to show this effect (Table 1). Interestingly, inflammatory markers like CRP and the pro-inflammatory cytokine interleukin-6 (IL-6) have also been shown to relate to specific symptoms of perimenopause, including hot flashes (Huang et al., 2017; Yasui et al., 2006) and sleep disturbances (Nowakowski et al., 2018; H. Zhang et al., 2021), although other studies failed to find links to vasomotor symptoms (Gold et al., 2022).

During perimenopause, prevalence rates also increase for several chronic medical conditions that often show sex differences, including risk for cardiovascular disease, autoimmune conditions like rheumatoid arthritis, type 1 diabetes, and certain cancers (Ben Shimol, 2023; Hoyt and Falconi, 2015). These conditions are often linked to or driven by immunologic and metabolic changes—and highly correlated with depression—further highlighting the critical need to understand the interplay between E2 and immune functioning in the context of perimenopause (McCarthy and Raval, 2020). Cardiovascular disease, in particular, has been linked to depression, with inflammation thought to play a mediating role (Mattina et al., 2019). Vascular alterations and increased endothelial dysfunction that arise during perimenopause may contribute to this increased risk (Mattina et al., 2019). It therefore remains critical to broaden our understanding of the multi-system changes that accompany perimenopause in order to identify potential avenues for intervention and protection.

4. Link between E2 and inflammatory pathways in depression

Estrogens, along with progesterone, are some of the primary forms of female reproductive hormones that circulate in the bloodstream and can cross the blood-brain-barrier (Schiller et al., 2016). E2 is the most prevalent form of estrogen prior to menopause (Cui et al., 2013; Herson and Kulkarni, 2022). Alongside its well-known reproductive effects, it is increasingly appreciated that E2 also plays an immunomodulatory role (Meltzer-Brody and Rubinow, 2021). E2 modulates nuclear factor kappa B (NF-κB) activity, which is critical for regulating proinflammatory genes (Monteiro et al., 2014). It can interrupt the production of type-I interferons (IFNs), an initial line of immune defense (Harding and Heaton, 2022). However, studies have also pointed to immune-stimulating effects of E2 (Asai et al., 2001). Indeed, translational research indicates that contradictory pro- and anti-inflammatory findings are plausibly due to expression of estrogen receptors (ERs) relative to inflammatory conditions, differential action of E2 on immune cell types, and circulating levels of E2 (Hoffmann et al., 2023; Straub, 2007). Together, these lines of evidence point to the complex dynamics between E2 and immune system functioning, rather than a straightforward pro- or anti-inflammatory effect of E2.

Outside of this literature on the immunomodulatory effects reproductive hormones, prior meta-analyses on associations between inflammation and depression have failed to find consistent variation in this association by sex (Mac Giollabhui et al., 2021). However, collapsing studies with broad age ranges may obscure potential effects.

Table 1
Studies of menopausal symptoms and inflammatory markers.

Author and year	Study population	Inflammatory markers	Notable findings
Associations with depression			
Figueroa-Vega et al. (2015)	60 early and late postmenopausal women	serum concentrations: ICAM-1, sVCAM-1, sCD62E, sCD62P, CSCL8, IL-1β, IL-6, TNF-α; expression of: CD62L, ICAM-1, PSGL-1, CD11b, CD11c, IL-8R	Depression negatively associated with PSGL-1 expression and positively associated with LPS-induced NO concentration.
Matthews et al. (2007)	3292 pre- and early perimenopausal women from SWAN	hsCRP, Factor VIIc, fibrinogen, PAI-1, tPA-ag	Higher depression symptoms associated with higher fibrinogen, PAI-1, tPA-ag, but not hsCRP.
Matthews et al. (2010)	1781 pre- and early perimenopausal women from SWAN followed through menopause transition	CRP	Higher CRP led to higher subsequent depressive symptoms.
Pasquali et al. (2018)	148 midlife women followed longitudinally (37 developed PO-MDD and 111 without)	HSP70, 3-Nitro-tyrosine, protein carbonyl levels, lipid peroxidation, BDNF, thiol content	PO-MDD development associated with increased HSP70, 3-nitrotyrosine, protein carbonyl, lipid peroxidation, and decreased BDNF.
Rudzinskas et al., 2021	lymphoblastoid cell lines from eight women with past PO-MDD and nine without	gene expression	Increased fold change compared to controls in: IGLL5, LAPTM4B, ITGAL, CCL17.
Liukkonen et al. (2010)	512 midlife women	hsCRP	Positive correlation between hsCRP and depression in peri and postmenopausal women not using hormones.
Metcalf et al. (2024)	142 midlife women from the POAS cohort	IL-6, IL-1β, TNF-α, hsCRP	Higher adverse childhood experiences and high current life stressors had stronger association between hsCRP and clinically significant depression.
Sturgeon et al. (2014)	34 pre and postmenopausal women with fibromyalgia	TNF-α, IL-6, IL-8, IL-10	Postmenopausal women have positive correlation between IL-8 and depression, but not premenopausal women. Greater depression associated with lower ratio of IL-6 to IL-10.
Karaoulanis et al. (2014)	65 perimenopausal women	HP, TRf, α1-antitrypsin, C3, cC4, and CRP	No difference in depressed vs nondepressed perimenopausal women

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Table 1 (*continued*)

Author and year	Study population	Inflammatory markers	Notable findings
Zainal and Newman (2023)	2224 women from SWAN	CRP	Higher CRP predicted greater depressed mood.
Harder et al. (2022)	14 perimenopausal women	BDNF, CRP, IL-6, TNF-α, TNF-R1, IP-10, and IL-1RA	BDNF significantly predicted mood symptoms, TNF-R1 significant negative predictor of POMS (Profile of Mood States).
Associations with other symptoms related to menopause			
Hot flashes			
Huang et al. (2017)	202 women ages 45-60	CXCL10, CCL2, CCL4, IFNG, TNF-α, IL-1β, IL-6, IL-8, IL-17a	Hot flash status positively associated with IL-6, IL-8, TNF-α, and CCL4.
Karaoulanis et al. (2014)	65 perimenopausal women	HP, TRf, α1-antitrypsin, C3, C4 and CRP	Hot flashes did not change levels of cytokines in perimenopausal depression.
Yasui et al. (2006)	129 pre-, peri-, and postmenopausal women and 50 bilateral oophorectomized women	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-α, granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, IFN-γ, MIP-1β, and monocyte chemotactic protein-1	Serum IL-8 and IL-1β higher in women with severe hot flashes compared to those without or with mild to moderate hot flashes.
Gold et al. (2022)	3302 women ages 42-52	hsCRP, IL-6	No significant association of hsCRP or IL-6, either concurrently or with subsequent incident VMS.
Sleep			
Huang et al. (2017)	79 perimenopausal women and 202 postmenopausal women	hsCRP, CXCL10, CCL2, CCL4, IFNG, TNF-α, IL-1β, IL-6, IL-8, IL-17a	Low sleep quality and efficiency associated with higher hsCRP, CXCL10, and IL-6; low sleep duration associated with high hsCRP.
Nowakowski et al. (2018)	295 peri and postmenopausal women	CRP, IL-6, VWF antigen	Lower sleep efficiency associated with higher IL-6 and VWF.
Zhang et al. (2021)	217 peri- and postmenopausal women	CRP, HYC, TG, TC, LDL, HDL, FINS	Levels of HCY, CRP, and lipids were significantly correlated with sleep quality in perimenopausal and postmenopausal women. HYC and CRP were identified as independent risk factors for sleep quality.

Note. BDNF - brain derived neurotropic factor; C3 - complement protein 3; C4 - complement protein 4; CRP - C-reactive protein; FINS - fasting insulin; HDL - high-density lipoprotein; HP - haptoglobin; hsCRP - high sensitivity CRP; HYC - homocysteine; IL - interleukin; INFG - interferon-gamma; LDL - low-density lipoprotein; MIP - macrophage inflammatory protein; PAI-1 - plasminogen activator inhibitor Type 1; TC - total cholesterol; TG - triglyceride; TNF-α - tumor necrosis factor-alpha; tPA-ag - tissue-type plasminogen activator antigen; TRf - transferrin; VWF - von Willebrand factor.

A recent review of sex hormones and the immune system by Lombardo and colleagues noted the relative dearth of studies specifically examining interplay between these factors and affective disorders (Lombardo et al., 2021). One study, however, found that levels of the pro-inflammatory cytokine IL-6 were prospectively associated with chronic course of a depression diagnosis at baseline in women but not men (Lamers et al., 2019).

In previously published work by this author (Bondy et al., 2021), inflammatory markers were associated with depressive symptoms approximately two years later in a mixed-sex sample of older adults. Although not directly tested in that paper, exploratory analyses within the sample indicate that women (n = 426) were characterized by greater levels of CRP, $t(767) = -4.194$, $p < 0.001$, and inflammatory cytokine tumor necrosis factor alpha (TNF-α), $t(648) = 2.536$, $p = 0.011$, compared to men. Notably, this sample of women was most likely postmenopausal (mean age = 65.97), although neither menopause status nor E2 levels were directly assessed in the study.

Interestingly, exogenous E2 (as opposed to naturally occurring endogenous E2) can also alter immune signaling. Hormonal replacement therapy (HRT) has been shown to exert anti-inflammatory effects (Figueroa-Vega et al., 2015; Harding and Heaton, 2022; Miller et al., 2003). HRT also demonstrates antidepressant effects (Garay et al., 2019; Maki et al., 2018; Rubinow et al., 2015), potentially through its effect on immune pathways implicated in depression (Engler-Chiurazzi et al., 2022; Vural et al., 2006). *In vitro* models of perimenopausal depression demonstrate proinflammatory genes were sensitive to E2 treatment and subsequent withdrawal (Rudzinskas et al., 2021). In the study mentioned above (Bondy et al., 2021), women who reported taking any form of hormone therapy (n = 37) had lower levels of IL-6, $t(408) = 3.532$, $p < 0.001$, and CRP, $t(412) = 2.007$, $p = 0.045$, compared to women without those medications. This may lend support to Lombardo and colleagues' claim that exogenous female reproductive hormones, such as HRT during perimenopause, may serve a protective role on the immune system (Lombardo et al., 2021). Others put forth a more nuanced interpretation, positing that HRT plays a moderating role between depression during perimenopause and inflammation (Liukkonen et al., 2010). Overall, the lack of studies directly testing these effects and the mixed results in extant studies point to the need for further clarification of the dynamics at play.

5. Directionality of E2-immune links

Although much research focuses on broadly immunomodulatory effects of E2, the relationship is likely not unidirectional. Alongside the growing body of work on the impact of E2 on immune system functioning, bidirectional relationships are also worth considering. Stress exposure may serve to suppress reproductive function, likely through its interaction with hypothalamic-pituitary-adrenal (HPA) and immune systems (Kalantaridou et al., 2004). Animal models suggest inflammatory stress, such as with an endotoxin of lipopolysaccharide (LPS), can disrupt the reproductive cycle through its effects on luteinizing hormone and subsequent E2 secretion (Karsch et al., 2002). Additionally, statin therapy to manage immune-related conditions such as cardiovascular disease lowers circulating E2 levels (Stamerra et al., 2021). However, many studies failed to find increased serum E2 levels in pre-, peri-, and postmenopausal women taking statins (Honjo et al., 1992; Peck et al., 2011; Ushiroyama et al., 2001). Given age-related increases in medical conditions and medications that impact the immune system that coincide with perimenopause, it will be important to investigate how E2 and inflammatory markers interact and influence one another.

6. Other sex hormones associated with immune function

This review focuses primarily on E2, although other reproductive hormones, such as progesterone, are linked to immune signaling. The neurosteroid allopregnanolone, a downstream metabolite of progesterone, blocks pro-inflammatory neuroimmune signaling through toll-like receptors (TLRs; Balan et al., 2019; 2021). Allopregnanolone levels drop during the transition to menopause, which correlates with depressive symptoms (Slopien et al., 2018). Additionally, perimenopause is associated with increases in androgen and its downstream substrate testosterone. Studies across men and women outside of perimenopause indicate lower testosterone is linked to increased expression of inflammatory markers, such as IL-6, IL-1, and TNF-α (Bianchi, 2019; Lorenz et al., 2017). Rising levels of testosterone, and more specifically the ratio between testosterone and E2, during perimenopause has been linked to increased depressive symptoms (Sander et al., 2021). Therefore, it will be critical for future work to comprehensively unpack immunologic associations across reproductive hormones that are fluctuating during this time.

7. E2 and neuroinflammation: a potential mechanism of action

As noted above (section **2.1**), E2 circulates throughout the body, including within the central nervous system (CNS), and it can also be synthesized within the brain (McEwen, 2002). It is thought to play a role in regulating metabolic function and cell differentiation, proliferation, and migration within the brain (Bustamante-Barrientos et al., 2021; Yin et al., 2015). Pre-clinical and human studies have identified the important role that E2 plays in neuroprotection through its stimulation of growth factors for neurite formation (Pozzi et al., 2006). The primary signaling of E2 occurs through estrogen receptors (ERs), which are present across the body (Monteiro et al., 2014). Two forms of ERs, ERα and ERβ, show differential localization across brain regions and may contribute to distinct cellular functions (Villa et al., 2016). These potential neuroprotective effects of E2 (Maggi et al., 2004) may be critically important as women age and enter perimenopause (McCarthy and Raval, 2020).

Unchecked immune activity within the CNS contributes to neurodegeneration and immune-related disorders (e.g., Alzheimer's disease, multiple sclerosis) linked to the phenomenon of neuroinflammation (Shabab et al., 2017). This activity is thought to be driven by chronic activation of microglia, the immune cells of the CNS which recruit circulating immune cells and clear debris from degeneration (Shabab et al., 2017). Animal models of neuroinflammation have indicated that microglial activation and immune gene expression can be impacted by E2 (Bruce-Keller et al., 2000; Vegeto et al., 2006). E2 works through ERs to block DNA binding and NF-κB transcriptional activity (Benedusi et al., 2012; Kalaitzidis and Gilmore, 2005).

As E2 levels drop across perimenopause and into menopause, neuroprotective capabilities likely decline and secretion of inflammatory factors and microglial activation can go unchecked by E2 (Liang et al., 2024; Vegeto et al., 2008). Preclinical studies support this notion; ovariectomized rodents show increased microglial reactivity in the context of reduced E2-mediated anti-inflammatory effects (Benedusi et al., 2012; Sárvári et al., 2012, 2012, 2012; Vegeto et al., 2006). Administration of exogenous E2 can attenuative this microglial activity in rodents (Sárvári et al., 2014). It remains unclear whether administration to peri- or post-menopausal women influences microglial activity, although results from postmortem brains indicate that administration of E2 upregulates ERβ expression in microglia (Li et al., 2000). Other studies have examined the effects of E2 on structural indices of neurodegeneration. During perimenopause, the CNS undergoes decreased glucose metabolism and reduced grey and white matter integrity (Barth and de Lange, 2020). Initial imaging studies in humans indicate that exogenous E2 administered as HRT may counter this volume loss (Erickson et al., 2005; Ha et al., 2007) and age-related white matter declines (Nabulsi et al., 2020), supporting the role of E2 in brain structure protection.

Preclinical studies suggest that neuroinflammation may contribute to the onset of depression in E2-deficient ovariectomized rodents (Park et al., 2020; Xu et al., 2016) and E2 can prevent depression-like behavior through targeting neuroinflammation (Najjar et al., 2018; W. Zhang et al., 2020). However, many studies of neuroinflammation in the context of perimenopause in humans have focused on other neurodegenerative disorders like Alzheimer's disease and Parkinson's dementia (Barrientos et al., 2019; Jett et al., 2022) rather than depression (Y. Han et al., 2023; Liang et al., 2024). Thus, it remains an intriguing avenue for future research to connect these findings with neuroinflammatory theories of depression that exist outside of the context of perimenopause (Bollinger, 2021; Furtado and Katzman, 2015; Gagne et al., 2022; Hurley and Tizabi, 2013).

8. Conclusion and recommendations for future research

Women's mental health research has long been overlooked, although emerging initiatives are working to address gaps in our knowledge. As the field of reproductive mood disorders gains momentum, it will be critical to shed light on *all* reproductive transitions, including perimenopause. Perimenopause has been proposed to be a "critical window" for identifying disease risk and intervening (Mosconi et al., 2017), although the specific timing of this window requires clarification (Nerattini et al., 2023). Historical exclusion of women from brain aging related research limit current conclusions, but more research is underway in this area. Independent lines of research reviewed here point to the widespread biological changes of the menopause transition and the subsequent impact on aging and health. However, a critical next step must be to bridge these findings into a comprehensive model to deepen our understanding of perimenopausal depression in particular.

The hypothesis of the interplay between hormones and immune mechanisms in contributing to neural and psychological changes during perimenopause remains an intriguing question for future research. Preclinical studies have provided important support for the proposed role of E2 in targeting neuroinflammation and depression. More neuroimaging studies in humans, using methods such as positron emission technology (PET) or diffusion based spectrum imaging (DBSI) to examine neuroinflammation in perimenopausal samples (Hu et al., 2023; Meyer et al., 2020). As the dynamics of E2 fluctuations vary across perimenopause, future studies should employ longitudinal designs (Pasquali et al., 2018) and experimental protocols (Walsh et al., 2023) to supplement existing cross-sectional work comparing groups of pre-, peri-, and postmenopausal women.

Of note, an in-depth consideration of the full spectrum of perimenopause-related changes and systems is beyond the scope of this review. Important biological factors, such as stress-related hypothalamic-pituitary-adrenal (HPA) axis dysregulation and the gut microbiome, as well as relevant psychosocial stressors, were not reviewed here but are undoubtedly intertwined with these pathways (Y. Han et al., 2023). Future work that comprehensively examines neuroendocrine, immunological, and psychological variables influencing the course of depression in perimenopause will be paramount to offering patients more targeted treatments and relief from distressing and often overlooked symptoms.

Funding

This work was supported by the National Institute of Mental Health (R01 MH128238).

CRediT authorship contribution statement

Erin Bondy: Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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